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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,706	04/10/2002	Guillermo De La Cueva Mendez	620-180	8608

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EXAMINER	
GANGLE, BRIAN J	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,706	DE LA CUEVA MENDEZ ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/14/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Sequence Requirements

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § § 1.821-1.825 for the reason(s) set forth below. Full compliance with the sequence rules is required in response to this office action.

This application fails to comply with the requirements of 37 C.F.R. 1.821-1.825 because it contains no sequence listing. 37 CFR 1.821(c) requires that applications containing nucleotide and/or amino acid sequences that fall within the above definitions, contain, as a separate part of the disclosure on paper or compact disc, a disclosure of the nucleotide and/or amino acid sequences, and associated information, using the format and symbols that are set forth in 37 CFR 1.822 and 37 CFR 1.823. This separate part of the disclosure is referred to as the "Sequence Listing." The "Sequence Listing" submitted pursuant to 37 CFR 1.821(c), whether on paper or compact disc, is the official copy of the "Sequence Listing." 37 CFR 1.821(e) requires the submission of a copy of the "Sequence Listing" in computer readable form. 37 CFR 1.821(f) requires that the official "Sequence Listing" (submitted on paper or compact disc pursuant to 37 CFR 1.821(c)) and computer readable copies of the "Sequence Listing" (submitted pursuant to 37 CFR 1.821(e)) be accompanied by a statement that the content of the official and computer readable copies are the same, at the time when the computer readable form is submitted.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d). Said papers have been placed of record in the file. The priority claim has been perfected.

Information Disclosure Statement

The information disclosure statement filed 1/14/2002 has been considered. An initialed copy is enclosed.

Election/Restrictions

Applicant's election with traverse of Group I in the response filed 10/19/2005 is acknowledged. The traversal is on the ground(s) that examination of all claims would not be an

undue burden. This is not found persuasive because burden is not a criteria in determining whether a restriction is proper when said restriction is made under PCT Rules 13.1 and 13.2.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting cell proliferation which include inhibiting cell cycle progression in eukaryotic cells *in vivo*, does not reasonably provide enablement for said method in all eukaryotic cells as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1 and 11 are drawn to methods of inhibiting cell proliferation by providing a bacterial toxin and an inhibitor of said toxin or optionally, an antidote to said toxin in eukaryotic cells. These claims encompass all eukaryotic cells which includes human cells and both *in vivo* and *in vitro* use of said method. The art has shown no examples of the claimed method being successful *in vivo*. The use of bacterial toxins alone, such as diphtheria toxin, has been proposed as a method of treating cancer, however, there have only been successes with *in vitro* studies or in mice models (Fitzgerald, Semin. Cancer Biol, 7:87-95, 1996, p. 93). Further, these studies involved injecting tumors with toxin, and did not follow the method of the instant application using an antitoxin or the specific embodiment of providing the toxin by expressing it within the cells. Diphtheria toxin has been used to control eukaryotic cell growth using transcriptional control elements, however, this work was only *in vitro* (Paulus *et al.*, J. Neurosurg., 87:89-95, 1997; Massuda *et al.*, Proc. Natl. Acad. Sci. USA, 94:14701-14706, 1997). The art also teaches

that while the use of toxins to control eukaryotic cell growth (esp. cancer) is promising, there are hurdles to be overcome. Vassaux *et al.* (Breast Cancer Res., 2:22-27, 2000) states that clinical use of genetic toxins would require efficient and reliable targeting of cancer cells, and that this cannot be achieved with current tools (p. 22, col. 1). Fitzgerald *et al.* states that two problems in particular must be overcome to use toxins. First, administration of toxins to humans has led to unanticipated toxicity in normal tissue, and second, the human immune response limits the effects of the toxin (p. 93, col. 1, paragraph 2). While the specification provides examples of the method using cells *in vitro*, there is no evidence to show that the method could be used successfully in humans. Further, the specification does not provide any basis for correlating the *in vitro* results with beneficial effects that could reasonably be expected when said toxins are administered *in vivo* to control cell proliferation in tumor or other cells, although *in vivo* use is clearly encompassed by the claims. The specification is lacking either direct evidence for *in vivo* benefit, or a reasonable basis for correlating the *in vitro* data as exemplified in the instant specification with *in vivo* benefit. Hence, the specification cannot be said to teach how to use the claimed toxins in all eukaryotic cells without undue experimentation. Moreover, while those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are somewhat useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to *in vivo* efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant

in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro). Moreover, Dermer (Bio/Technology, 1994, Vol. 12 page 320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interactions. In view of the lack of support in the art and specification for the use of the method with all eukaryotic cells, it would require undue experimentation to use the full scope of the method as claimed; therefore the entire scope of the claim is not enabled.

Claims 4 and 7-9 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As to claim 4, the claim is drawn to a method of claim 1 which is therapeutic and carried out on a human or animal body. The art has shown no examples of such a method being successful. The use of bacterial toxins alone, such as diphtheria toxin, has been proposed as a method of treating cancer, however, there have only been successes with *in vitro* studies or in mice models (Fitzgerald, Semin. Cancer Biol, 7:87-95, 1996, p. 93). Further, these studies involved injecting tumors with toxin, and did not follow the method of the instant application using an antitoxin or the specific embodiment of providing the toxin by expressing it within the cells. Diphtheria toxin has been used to control eukaryotic cell growth using transcriptional control elements, however, this work was only *in vitro* (Paulus *et al.*, J. Neurosurg., 87:89-95,

1997; Massuda *et al.*, Proc. Natl. Acad. Sci. USA, 94:14701-14706, 1997). The art also teaches that while the use of toxins to control eukaryotic cell growth (esp. cancer) is promising, there are hurdles to be overcome. Vassaux *et al.* (Breast Cancer Res., 2:22-27, 2000) states that clinical use of genetic toxins would require efficient and reliable targeting of cancer cells, and that this cannot be achieved with current tools (p. 22, col. 1). Fitzgerald *et al.* states that two problems in particular must be overcome to use toxins. First, administration of toxins to humans has led to unanticipated toxicity in normal tissue, and second, the human immune response limits the effects of the toxin (p. 93, col. 1, paragraph 2). The only guidance the specification provides is to state that compositions of the toxin-antitoxin may be administered to individuals, preferably in "therapeutically effective amounts." The specification further states that the amount, rate, and time-course of administration will depend on the nature and severity of what is being treated (p. 33. lines 5-15). There are no examples or data to show any therapeutic effect of any embodiments of the present invention, either in an animal model, or humans. In view of the lack of support in the art and specification, it would require undue experimentation to use the method as claimed; therefore the claim is not enabled.

As to claim 7, and dependent claims 8-9, claim 7 is drawn to a method of inhibiting cell proliferation by providing a bacterial toxin and an inhibitor of said toxin within eukaryotic cells, wherein said toxin targets *DnaB*. The only example of a toxin given in the specification that would allegedly meet said limitation is the Kid toxin. The specification states that over-expression of *DnaB* titrates the toxic effect of Kid in *E. coli*, suggesting that *DnaB* is involved in the mechanism of inhibition by Kid (p. 8, lines 10-20). However, the specification teaches that Kid is capable of inhibiting growth of eukaryotic cells, including *Saccharomyces*, *Xenopus*, and human cells. *DnaB* is not found in those cells, and is only found in a few eukaryotic species. This would suggest that inhibition of *DnaB* is not the mechanism through which Kid inhibits cell proliferation. The art further suggests that *DnaB* is not the target of Kid. Diaz-Orejas *et al.* (ELSO Gazette, 17:1-9, 2003) state that though Kid was initially thought to target *DnaB*, further experiments do not fit this hypothesis. Kid failed to inhibit the helicase activity of *DnaB* (p. 6, col. 2, paragraph 2). There are no toxins that target *DnaB* disclosed in either the art or the specification. In light of the teachings of the art and the specification, it would require undue experimentation to use the method of the instant invention; therefore the claim is not enabled. It

is noted, however, that the subject matter of claims 8-9 would be enabled if the claims were not dependent on claim 7.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 1, dependent claims 2-10, and 12-16, claim 1 recites "a method of inhibiting cell proliferation and/or cell cycle progression." The method steps require providing a toxin within eukaryotic cells, whereas the preamble is directed to cells in general, not only eukaryotic cells. Further, The term "target cells" lacks antecedent basis, thus it is unclear what a target cell is. Also, the claim recites "an inhibitor of said toxin, optionally and antidote to the toxin wherein both toxin and antidote are proteins, under appropriate control for cell cycle inhibition." It is unclear what "appropriate control" refers to. Is the "appropriate control" optional, and is the antidote, inhibitor, or toxin under appropriate control? Additionally, how is an antidote different from an inhibitor? An antidote would necessarily inhibit the toxin.

As to claim 1, dependent claims 2-10, and 12-16, claim 1 recites "a method of inhibiting cell proliferation and/or cell cycle progression." Is there a case where inhibiting cell cycle progression does not include inhibiting cell proliferation?

As to dependent claims 2-10 and 12-17, the claims are confusing because they recite the indefinite article "A" meaning any product or method, but then attempt to limit the method/product to a particular product form or method steps. Amendment of the claims to change "A" to "The" would obviate this issue.

As to claim 11 and dependent claims 12-17, claim 11 recites "a method of inhibiting cell proliferation and/or cell cycle progression." The method steps require providing a toxin within eukaryotic cells, whereas the preamble is directed to cells in general, not only eukaryotic cells.

As to claim 12 and dependent claims 13-16, claim 12 recites "controlling activity of said antidote on said toxin to control activity of said toxin on said cells." It is unclear whether "controlling activity of said antidote" is meant to be an active step or a further limitation of the "appropriate control" in claim 1. Further, "controlling activity" lacks antecedent basis since the

specification only provides for a means of controlling the presence and amount of the antidote, which in turn controls the activity of the toxin, not a means of controlling the activity of the toxin.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 and 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Molin *et al.* (US Patent 5,670,370, 1997).

As to claims 1-6 and 10-11, Molin *et al.* disclose a method of inhibiting cell proliferation and/or cell cycle progression, where the method comprises providing within plant, or other eukaryotic cells (col. 5, lines 4-10), a replicon which encodes a cell-killing function and an inhibitor of said cell-killing function (col. 4, lines 55-65; col. 6, lines 14-25). The replicon disclosed encodes a toxin (*hok*) of a post-segregational killing system which is inhibited by antisense RNA (col. 10, 25-28; col. 9, lines 14-16). Said method is disclosed for use *in vitro* in a fermentation vessel (col. 5, lines 27-35). This method is also a therapeutic method (col. 13, lines 32-36). As to claim 6, the claim is drawn to the method of claim 1 where the toxin interferes with DNA replication, thereby impeding cell cycle progression. The toxin used in the method disclosed by Molin *et al.* will cause cell death, which prevents DNA replication and cell cycle progression.

Claims 1, 2, 6, 10, and 12-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Paulus *et al.* (J. Neurosurg. 87:89-95, 1997).

As to claims 1, 2, 6, 10, and 12-16, Paulus *et al.* disclose a method of inhibiting tumor cell proliferation comprising providing within the cells the nucleic acids encoding diphtheria

toxin (DTA) and a control system where the lacR protein inhibits production of DTA (p. 90, col. 1, paragraphs 2-4). The method uses human glioblastoma cells and was performed *in vitro* (pp. 90-91, materials and methods). The toxin used in the method disclosed by Paulus *et al.* will cause cell death, which prevents DNA replication and cell cycle progression. In the lacR control system of the method, expression of DTA is abolished when lacR binds the lacO sequence and is restored upon addition of IPTG (p. 92, col. 1, paragraph 2).

Status of the Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Gangle whose telephone number is 571-272-1181. The examiner can normally be reached on M-F 8:00 am - 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Brian Gangle
AU 1645

ROBERT A. ZEMAN
PATENT EXAMINER